

Chemistry of Some Amino Acid Derivatives of 2,2-Dichloropropionic and 2,3,6- Trichlorobenzoic Acids

THIS report describes the preparation, purification, and properties of 18 new herbicides, amino acid derivatives of 2,2-dichloropropionic acid (dalapon) and 2,3,6-trichlorobenzoic acid (2,3,6-TBA). The biological evaluation of the compounds as selective herbicides is being made by other investigators and will be published later. Some of the compounds are also being evaluated for nematocidal, fungicidal, and anticancer properties.

Previous experience with a variety of chlorine substituted phenoxy acids has demonstrated that amino acid attachment through amide linkage can substantially affect the selective herbicidal and growth-regulating properties of phenoxy compounds^{2, 3} (2, 3, 4, 5, 6, 8). In these studies it was found that plant growth regulation depended, not only upon the amino acid and phenoxy acid coupled, but it also depended upon the optical configuration of the compounds prepared; hence, the reasons for preparing these two series with the use of several amino acids in their *D*-, *L*-, and *DL*-configurative forms.

A. AMINO ACID DALAPON COMPOUNDS

As a herbicide, dalapon is generally more toxic to monocotyledonous than to dicotyledonous plants. Because of this property, the compound is most widely used in the control of grasses in agronomic and horticultural crops. The limiting factor with respect to the merit of dalapon in its many applications is its phytotoxicity. Derivatives of dalapon having lower toxicity and greater selectivity would be desirable.

Of the series of derivatives reported here, only one compound, N-(2,2-dichloropropionyl)-*L*-leucine, has been evaluated for herbicidal properties so far.⁴ In post-emergence spray applications responses of crop plants to this derivative were more pronounced in 11, less pronounced in 7 plants. In 7 weed species tested the amino acid derivative was more toxic to 4 species, less toxic to 1 species, than the parent dalapon.

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²Unpublished data. Shaw, W. C. and Gentner, W. A., Weed Control in Crops Section, Crops Research Division, ARS, USDA, Plant Industry Station, Beltsville, Md.

³Krewson, C. F., Carmichael, J. F., Drake, T. F., Mitchell, J. W., and Smale, B. C., "Growth regulators. Synthesis and preliminary evaluations of amino acid derivatives of *DL*-2-(2,4,5-trichlorophenoxy)-propionic acid."

⁴Gentner, W. A., and Shaw, W. C. An evaluation of several chemicals for their herbicidal properties—1958 field results. USDA Progress Report. CR-6-59. ARS. Plant Industry Station, Beltsville, Maryland. 59 pp. January 1959.

Synthesis of amino acid derivatives of dalapon.

In order to chemically unite an amino acid through an amide linkage to dalapon it was first necessary to convert the latter to its chloride, 2,2-dichloropropionyl chloride.

2,2-Dichloropropionyl chloride (I). This compound was prepared in 87.1% yield by the reaction of dalapon⁵ (3.0 M) with thionyl chloride (4.0 M) by the method of Freed (1). The acid chloride distilled at 36–40°/0.6–0.8 mm., n_D^{25} 1.4540.

Anal. Calcd. for $C_3H_3Cl_2O$: Cl, 65.8% Found: Cl, 64.7%.

Either of the following two general procedures (2, 7) were used in the preparation of the amino acid derivatives. The Ronwin technique (7) was used only for the *D*- and *L*- threonine derivatives. The amino acids used were of the best quality obtainable from commercial sources.

N-(2,2-Dichloropropionyl)-D-leucine (II). To 13.1 g. (0.1 M) of *D*-leucine dissolved in 200 ml. (0.3 M) of 1.5 N sodium hydroxide solution was added dropwise a solution of 16.1 g. (0.1 M) of I dissolved in 150 ml. of benzene. The reaction mixture was chilled to 5° and stirred mechanically. Upon complete addition the ice bath was removed and the mixture stirred for an additional 3 hours as it warmed to room temperature. The reaction mixture was extracted with ethyl ether and the ether extracts combined and washed with 100 ml. of distilled water. The water wash was separated and added to the alkaline aqueous solution of the product which was then acidified to a pH 3 with 1 N hydrochloric acid. A white precipitate resulted during the addition of the hydrochloric acid. After cooling this mixture in the refrigerator for 2 hours, the precipitated product was extracted with ethyl ether. The ether solution was washed with water and dried over anhydrous calcium sulfate. The ether solution was filtered and the solvent removed using an air current. The vacuum dried crude material weighed 18.0 g (70.3%), m.p. 100–104° (Kofler micro melting point apparatus). Crystallization from hot ethyl acetate using petroleum ether (b.p. 63–70°) as a precipitating agent gave 14.0 g. (54.6%) of pure II, m.p. 104.0–105.0°.

Anal. Calcd. for $C_9H_{15}Cl_2NO_3$: Cl, 27.68%; N, 5.46%. Found: Cl, 27.24%; N, 5.53%.

N-(2,2-Dichloropropionyl)-D-threonine (III). To 10.6 g. (0.08 M) of *D*-threonine suspended in 200 ml. of ethyl acetate was added 12.9 g. (0.08 M) of I dissolved in 100 ml. of ethyl acetate. The reaction mixture was refluxed for 30 hours as it stirred mechanically. The warm reaction mixture was filtered and the solvent evaporated leaving an oil. Repeated slurring of the oil with petroleum ether gave a white solid. The vacuum dried crude material weighed 9.0 g. (46.1%), m.p. 115.0–120.0°. Crystallization from hot ethyl acetate-petroleum ether and from methylene chloride-petroleum ether gave 6.9 g. (35.3%) of pure III, m.p. 118.5–120.0°.

⁵Supplied through the courtesy of the Dow Chemical Company, Midland, Michigan. Mention of commercial products or names does not imply that they are endorsed or recommended by the Department of Agriculture over others of a similar nature not mentioned.

<i>N</i> -(2,2-dichloropropionyl)-	M.P. (corr.) ^a	Yield, %		Analyses ^b					
				Cl, %		N, %		Optical rotation ^c [α] _D ²⁵	
		Crude	Refined	Calcd.	Found	Calcd.	Found		
<i>L</i> -leucine	104.0–106.0 ^d	76.1	44.0	27.68	27.50	5.46	5.47	–6.33 ± 0.4	
<i>D</i> -leucine	104.0–105.0	70.3	54.6	27.68	27.24	5.46	5.53	+7.03 ± 0.4	
<i>DL</i> -leucine	85.0–86.0 ^e	82.7	26.1	27.68	27.16	5.46	5.49		
<i>L</i> -methionine	55.0–56.5 ^f	71.5	31.7	25.87	26.00	5.13	5.14	–3.37 ± 0.4	
<i>D</i> -methionine	52.0–55.0	58.0	35.1	25.87	25.58	5.13	5.06	+2.19 ± 0.4	
<i>DL</i> -methionine	56.0–58.0	35.5	25.9	25.87	25.66	5.13	5.07		
<i>L</i> -threonine	124.0–125.0	48.3	16.5	29.05	28.86	5.73	5.73	–14.2 ± 0.4	
<i>D</i> -threonine	118.5–120.0 ^g	46.1	35.3	29.05	28.94	5.73	5.81	+13.55 ± 0.3	
<i>DL</i> -threonine	180.0–182.0 ^h	—	17.5	29.05	29.45	5.73	5.69		

^aRecrystallized one or more times from ethyl acetate-petroleum ether unless otherwise indicated.

^bAnalyses by J. S. Ard.

^cConcentration 2.00 g./100 ml. in pyridine.

^dAs in a; also from benzene-petroleum ether.

^eRecrystallized from petroleum ether only.

^fAs in a; also from petroleum ether.

^gAs in a; also from methylene chloride-petroleum ether.

^hNo recrystallization necessary.

B. AMINO ACID DERIVATIVES OF 2,3,6-TRICHLOROBENZOIC ACID

Recently Gentner and Shaw⁶ reported on the comparative herbicidal activity and selectivity of 14 variously substituted benzoic acids or derivatives. All of these were tested on 26 crop plants and weed species as pre-emergence and 12 were tested as post-emergence sprays. A *L*-leucine derivative of 2,3,6-TBA, the only amino acid compound of this new series tested to date, reduced the activity of the highly active moiety of 2,3,6-TBA in both pre- and post-emergence applications. This suggested the possibility of tailor-making specificity and selectivity into the 2,3,6-TBA molecule with amino acids.

Synthesis of 2,3,6-trichlorobenzoic acid derivatives.

Schotten-Baumann procedures similar to those previously described (4, 8) were employed in the preparation of amino acid derivatives of 2,3,6-TBA. The 2,3,6-TBA was supplied as a solution of the dimethylamine salt⁷ (4 lb/gal). To effect precipitation of the 2,3,6-TBA this solution was adjusted to pH 2 with 10% hydrochloric acid solution. The 2,3,6-TBA was then filtered off and recrystallized twice from hot toluene and once from hot petroleum ether (b.p. 63–70°); m.p. 2,3,6-TBA 135.5–138°.

⁶Gentner, W. A., and Shaw, W. C. *loc. cit.*⁴

⁷Supplied by R. W. Varner of E. I. duPont de Nemours and Company, Wilmington, Delaware.

2,3,6-Trichlorobenzoyl chloride. The purified 2,3,6-TBA was converted to its corresponding chloride by the method of Freed (1). A yield of 96% was obtained with a 0.5 M quantity of 2,3,6-TBA and 1.5 M thionyl chloride; boiling point of product 68–69° at 0.2 mm., n_D^{26} 1.5900.

Anal. Calcd. for $C_7H_2Cl_4O$: C, 34.46%; H, 0.83%; Cl, 58.15%. Found: C, 34.52%; H, 0.59%; Cl, 58.11%. Product has remained a clear stable liquid after 9 months' storage at 5°. The following illustration exemplifies the procedure used for the preparation of all the amino derivatives of 2,3,6-TBA.

N-(2,3,6-trichlorobenzoyl)-L-leucine. A 0.5 M quantity (65.5 grams) of *L*-leucine was dissolved in 1500 ml. of 1.0 M sodium hydroxide solution and chilled to 5°. A 0.5 M quantity (122.0 grams) of 2,3,6-trichlorobenzoyl chloride was dissolved in 1500 ml. of benzene and chilled to 5°. The benzene solution was added dropwise during continuous stirring to the alkaline solution of *L*-leucine. The temperature was maintained at 5°; the time required for complete addition of the benzene solution was about 1 hour. The reaction mixture was stirred an additional 3 hours as it warmed up to room temperature. Three ethyl ether extractions were made of the alkaline reaction mixture using 500, 250 and 250 ml. portions of ether. These ether extracts were combined and washed once with 200 ml. of distilled water. This wash water was added to the ether extracted aqueous alkaline reaction mixture and the solution (pH 10.4) was adjusted to a pH of 1.2 with 10% hydrochloric acid; it was allowed to stand for 20 hours at 5°. The crude white crystalline product was filtered off, slurried several times with distilled water, filtered off and vacuum dried at room temperature to constant weight, crude yield 135.0 grams (79.5%).

Purification consisted of extracting in a Soxhlet apparatus for about 20 hours with petroleum ether (b.p. 63–70°) to remove unreacted 2,3,6-TBA; purified yield 122.6 grams (72.3%).

The *D*-leucine, *L*-methionine and *D*-, *L*-, and *DL*-threonine derivatives were purified in the same manner.

Crude *DL*-leucine and *DL*-methionine derivatives were recrystallized from hot ethyl acetate-petroleum ether; the crude *D*-methionine received the same treatment plus one recrystallization from dilute ethanol followed by washings with hot petroleum ether. The crude *DL*-threonine derivative was recrystallized from hot petroleum ether (b.p. 95–127°).

Information on yields, properties and analyses of the 9 amino acid derivatives of 2,3,6-TBA prepared is presented in Table 2. The melting points of some of these compounds were indefinite and in several instances were not improved by additional recrystallizations.

RESULTS AND DISCUSSION

In the preparation of the amino acid derivatives of both dalapon and 2,3,6-TBA most of the compounds in the crude state separated from reaction mixtures as crystalline white solids. Occasionally instead of a white solid an oil was obtained which crystallized on

Table 2: Yields, physical properties and analyses of amino acid derivatives of 2,3,6-trichlorobenzoic acid.

<i>N</i> -(2,3,6-dichlorobenzoyl)-	M.P. (corr.)	Yield, %		Analyses ^a					Optical rotation ^b [α] _D ²⁵
				Cl, %		N, %			
		Crude	Refined	Calcd.	Found	Calcd.	Found		
<i>L</i> -leucine	129-132	79.5	72.8	31.42	31.58	4.14	4.09	-4.23	
<i>D</i> -leucine	148-160	88.5	78.9	31.42	31.70	4.14	4.10	+11.43	
<i>DL</i> -leucine ^c	95-102	52.8	37.9	31.42	29.88	4.14	2.95	+0.06	
<i>L</i> -methionine	Indefinite	30.8	20.7	29.82	29.86	3.93	3.94	-2.40	
<i>D</i> -methionine	60-65	81.3	60.8	29.82	29.82	3.93	3.71	+6.50	
<i>DL</i> -methionine	Indefinite	45.7	27.5	29.82	29.49	3.93	3.86		
<i>L</i> -threonine	Indefinite	10.7	4.9	32.57	33.10	4.29	3.13	+21.03	
<i>D</i> -threonine	Indefinite	26.0	15.0	32.57	32.46	4.29	4.18	-22.74	
<i>DL</i> -threonine	161.164	27.8	27.7	32.57	32.31	4.29	4.28		

^aAnalyses by J. S. Ard.

^bConcentration 3.00 grams/100 ml. in pyridine; error estimated to be less than $\pm 0.3^\circ$.

^cPurity considered acceptable because of a 2.99 chlorine/nitrogen ratio compared to a calculated value of 3.00.

prolonged standing at about 5° C. When these did not crystallize they were thoroughly washed with water after decanting the original mother-liquor. When evacuated to constant weight at room temperatures these oils turned to amorphous solids and could then be purified by the usual procedures.

Since the amino acid derivatives of dalapon have subsequently been found to possess moderate water solubility this may account for the low yields obtained in their preparation, especially by Schotten-Baumann techniques. Also, the low yields obtained for the threonine derivatives of 2,3,6-TBA may be for the same reason since they possess considerable water solubility.

No attempts were made to improve yields either by working up mother-liquors or by recovering products from petroleum ether extracts in purification procedures. Reduction in water volumes used in Schotten-Baumann reactions where water solubility is a contributing factor should result in improved yields.

SUMMARY

1. Nine dalapon and nine 2,3,6-TBA amide derivatives of amino acids have been synthesized using the *D*-, *L*- and *DL*- configurative forms of leucine, methionine, and threonine.

2. Most of these compounds were readily prepared, purified and analyzed. Where sharp melting points, and characterizing rotations for *D*- and *L*- optical forms, prevail such derivatives may be useful in the identification of amino acids.

3. Preliminary field tests on *L*-leucine derivatives of dalapon and 2,3,6-TBA have shown the pronounced effect of amino acid coupling upon the selectivity pattern of the parent compounds. These results are in close agreement with past experiences concerned with amino acid compounds of phenoxy herbicides.

4. Biological evaluation of the compounds as selective herbicides

is being made by other investigators and will be published later. Some of the compounds are also being evaluated as nematocides, fungicides, and as anticancer agents.

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